The Significance of Infection in Allergic Disease

Its Influence on Diagnosis and Management

RALPH BOOKMAN, *M.D.*, and RICHARD S. SHAPIRO, *M.D.*, Beverly Hills

• **The presence of infection in allergic disease produces a confused picture in which two different causative factors must be clearly separated by the physician if he is to treat the patient successfully. The effects of infection are not consistent. There are situations, as seen in infectious diseases, where symptoms of allergic disease are temporarily relieved and others where the infection may intensify or precipitate the allergic condition. It is likewise important to recognize the complications superimposed upon allergic disease by infection. In such cases, control of the infection is as dependent upon control of the allergy as it is upon antibiotics.**

THE DEVELOPMENT of concurrent infection in allergic disease produces a double effect because not only is the pattern and course of the allergic disease altered but, reciprocally, the infection is also thereby modified. This ambivalent circumstance can produce diagnostic and therapeutic confusion and can also lead to the convenient premise that infection is the cause of the entire clinical manifestation unless the interrelationships are understood. Available evidence and clinical experience does not support this belief.

Misunderstanding develops from a failure to specifically limit definition of the term *allergy* to clinical considerations wherein such organs as the respiratory tract or the skin manifest allergic disease and almost invariably respond to specific treatment. Broad use of the term *allergy* to include the immune reaction to tuberculin or to such vaguely understood areas as collagenous disease, has no place here. We shall confine our remarks, therefore, to the clinical conceptions of allergic disease as commonly encountered in everyday practice and which are involved with but not caused by infection. Although the two may seem inseparably related, they must be recognized as separate and treated individually.

Today's concept of infection recognizes its systemic effect in addition to the local focus of inflammatory response. Fever, lymph nodal enlargement, cellular changes in organs with alteration of function and concurrent changes in pituitary and adrenal gland responses attest the constitutional impact of both viral and bacterial disease. This general responsiveness and change necessarily has an effect upon an allergic person, for his disease is also a constitutional one even though the apparent manifestations are focussed in one area or shock organ. With infection the local response tends to be the focal point of the cause whereas in allergic disease the local response is secondary to a systemic cause. It is not unusual, therefore, to find that symptoms of allergy are altered by infection just as infection can be exaggerated or intensified when it develops upon the stroma of allergic disease. It is the variable role that infection plays which must be recognized and understood in order to place it in its proper perspective.

The episode or attack of allergic disease which accompanies or is precipitated by infection is most commonly encountered in practice. Since the life history of an allergic person is punctuated by exacerbations and remissions of symptoms, it is not unusual to find the onset of some episode initiated by the development of an acute infection. An attack of asthma may be associated with such a sequence, yet a detailed history will uncover previous asthma or other allergic symptoms indicating that this attack was not de novo. The onset of prolonged exacerbations of allergic rhinitis, particularly during the winter months, sometimes will start with an infection manifested by fever and purulent nasal drainage for a few days. The nocturnal cough which persists long after such an onset similarly connotes a postnasal drip from an allergic nasal mucosa.

The idea of an infectious onset is commonly misapplied to bronchial asthma. Nasal symptoms—obstruction, sneezing and rhinorrhea—will often characterize the early phases of this condition. In describing this sequence of events the patient may misdirect attention to a non-existent upper respiratory tract infection rather than to the asthma itself. It is advisable to insist upon an explicit definition of the word "cold" which is so loosely applied

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to respiratory symptoms of all varieties. Similar diagnostic confusion develops because chronic respiratory symptoms are too readily diagnosed as bronchiectasis. Allergists encounter few such cases in which that diagnosis can be thoroughly substantiated. Patients with that diagnosis may have bronchial asthma and thrive therapeutically when so treated. At the Long Beach Veterans Hospital a survey of patients who had been labeled in other centers as having bronchiectasis produced relatively few valid cases when subjected to critical review. Radiologists in a large local hospital who were questioned on this subject said that bronchiectasis as a radiological diagnosis is very unusual in their experience.

These observations suggest that greater caution is needed in assessing chronic respiratory disease. In particular it should be recognized that such chronic symptoms as are accompanied by considerable expectoration of sputum should be suspect for bronchial asthma before consigning them to the more dismal prospects often associated with bronchiectasis. Finally, it is important to recognize the mild, superficial bronchitis which occasionally complicates asthma and is accompanied by purulent sputum, minimal systemic symptoms and a prompt response to expectorants and to antibiotic therapy.

Some infections suppress rather than potentiate allergic disease. This is particularly true of the viral diseases, for symptoms of allergic reaction diminish or even vanish entirely under their influence.[3] Such observations are common during the infectious diseases of childhood. Although the exanthem of chicken pox, for example, may be quite intense in an eczematous patient, is is reassuring to the parent to know that the allergic rash tends to subside. There seems to be no direct connection between this suppressive effect and the clinical intensity of the viral disease. Part of this pattern is the brief exacerbation of allergic disease during the invasion period of infectious disease. This will usually evaporate as full blown symptoms develop. It is possible that the relationship is a type of immunological inhibition or is perhaps related to the stress phenomenon which accompanies invasion of a virus. This symptom pattern was noted by us during a recent epidemic of influenza as well as during brief episodes of viral enteritis. One of us[2] reported the suppression of eczema during the course of Kaposi's varicelliform eruption, a disease most often caused by the virus of herpes simplex. Recognition of this relationship, therefore, is essential if the physician is to anticipate events and reassure the patient or parent.

Conversely, upon examination of the effect of allergic disease upon infection, it is observed not only that the infection can be intensified but that in almost all such situations it is the respiratory tract that is affected. When this occurs, adequate drainage of secretions is essential if infection is to resolve promptly. The patient with allergic disease of the respiratory tract must dispose of excessive secretion of mucus from the sinuses, the nasal mucosa or the bronchi. Interference with this evacuation, whether by edema or inspissated mucus, leads to stasis and encourages the development of secondary infection, and treatment of both the allergic obstruction and the infection becomes necessary.

A number of typical examples may be cited. Sinus infection must generally be regarded as developing in this fashion, and it has been reported that the infection in this instance is usually superimposed upon mucosa altered by allergic response.[9] The same investigator found the sinus infection quite superficial, suggesting that adequate drainage could be the primary ingredient of a cure.

In such circumstances the effect of surgical treatment is, at best, to provide temporary relief while by-passing the underlying allergic cause. The only indication for surgical interference in the nose in the vast majority of cases of sinus infection or even of simple airway obstruction is the presence of obstructive nasal polyps. Middle ear infection in many instances is secondary to allergic edema of the fossa of Rosenmuller that closes the eustachian orifice. The presence of lymphoid or adenoid tissue in this area in children explains their increased susceptibility, since such tissue swells easily. If the obstruction is not relieved soon after the initial symptom of ear pain, secondary infection develops rapidly. In bronchial asthma a very serious sequence of events attends the obstruction of a bronchus by a plug of inspissated mucus. That area of lung beyond the plug becomes atelectatic and pneumonitis develops rapidly. One can observe the tremendous importance of obstruction in such cases when dramatic evaporation of clinical evidence of infection is produced by expulsion of the mucus plug. Here again it is apparent that treatment of the infection alone is insufficient. One of the dangers inherent in all these examples of infection incident to allergic obstruction is the tendency for the acute infection to so obscure the allergic component that the physician's attention is drawn exclusively to the infection.

When the skin is involved in allergic disease, secondary infection is relatively uncommon even in the presence of impetiginous lesions of the unaffected skin.[1] One can infer that the eczematous skin must be particularly resistant, since it is subjected to constant trauma and excoriation of scratching with dirty hands. Occasionally, a simple pustular eruption becomes superimposed and responds rapidly to antibiotic therapy. Chronic, low grade infection is also seen now and then with local enlargement

of lymph nodes as its cardinal characteristic. While the suppressive effect of viral disease has already been mentioned in this regard, viral involvement of the eczematous skin is sometimes seen and can be very serious. The virus of both herpes simplex and vaccinia invade areas involved in eczema, producing Kaposi's varicelliform eruption. No specific therapy is available for this disease, which can be attended by pronounced toxicity and, occasionally, by death. It is therefore a very important prophylactic measure not only to withhold vaccination from patients with eczema but also for such patients to avoid exposure to herpes simplex.

Occasionally an allergist is consulted regarding unknown fevers, and in some such cases a rather typical but obscure syndrome may be found. The patient with this syndrome is invariably a child with perennial nasal symptoms and long periods of elevated temperature lasting for weeks or even months. Exhaustive investigation for the cause of the fever produces no etiologic clues and extensive use of antibiotics proves fruitless, and the nasal symptoms are patently of allergic origin. We are currently treating two such children by specific hyposensitization injections who are now able to attend school regularly whereas they had previously required home tutors because of prolonged absences due to persistent fever. The diagnostic obscurity of these cases and the failure of all other therapeutic efforts is ample justification for management directed at relief of allergic response when evidence of allergic disease exists.

Consonant with the foregoing remarks it should be apparent that concomitant allergic disease and infection require a therapeutic program which considers both factors. It is unfortunate that the concept that infection is a cause of allergic disease still exists, for it thwarts effective therapy. Siegal studied 109 asthmatic patients with sinus disease and came to the conclusion that the infection was not causally related but merely superimposed upon the associated upper respiratory tract allergic disease.[9] Hosen and Carabelle observed a large group of patients and concluded that in no case at any age could infection be labeled as a cause of allergic disease, although they regarded it as being of considerable importance as a secondary or trigger mechanism.[7] Because allergy is etiologically independent of infection, the use of bacterial vaccines is illogical and ineffective. Well controlled studies on large numbers of patients with asthma showed unequivocally that no better results are obtained with vaccine therapy than with injections of saline solution used as controls.[4] Helander, who used a double-blind format for his investigations, pointed out the danger of local and systemic reactions to injections of bacterial vaccines which he considered as more dangerous and certainly far less effective than specific hyposensitization.[6] Any apparent connection between vaccine injections and successful results must be classified as either a placebo effect or as a nonspecific protein reaction which for many years has been known to be of some slight value in the treatment of allergic disease.

The importance of drainage in infections of the allergically involved respiratory tract cannot be overemphasized. Involvement of the nasal passages and sinuses calls for the use of decongestants, which should be mild and buffered to avoid further irritation. Too frequent use of powerful or irritating solutions in the nose will cause a subsequent and more severe edema. Antihistamines will augment decongestion but seem to lose their effectiveness in the presence of inflammation. The relative potency of these drugs varies with the individual patient and they must be tried on this basis. Liberal quantities of decongestant should be used early in acute otitis media in an effort to open the eustachian tube orifice. At least 1 cc. should be instilled, with the head tilted to be certain that the solution reaches the part. When effective, this should be repeated at three-hour intervals to maintain patency. Drainage of the bronchial tree involves a different therapeutic approach. Particularly, antihistamines should be avoided, as they have drying action which encourages mucus plugging.[10] Efforts should rather be directed toward thinning and softening the mucus secretions and encouraging their evacuation by cough. Nothing has been found more effective for this purpose than the liberal ingestion of fluids. This must be dramatically impressed upon the patient, with intravenous administration offered as the only alternative. To implement the effect of fluids, potassium iodide in saturated solution stands alone as an efficient expectorant regardless of proprietary claims. The use of agents that suppress cough is obviously antagonistic to these principles and must be avoided.

Antibiotics are unquestionably effective as a part of the therapeutic regimen but their use in uncomplicated allergic disease and as prophylaxis has proved to be of little value. More complications and longer illnesses develop when antimicrobial agents are used to prevent infection, according to Reimann.[8] It is therefore mandatory to assess respiratory symptoms carefully and to seek supportive evidence of infection such as fever and increased leukocyte content in the blood. Combinations of antibiotics should be avoided since their effect is rarely additive and there is strong evidence that some may be less effective than when given alone.[8] In particular, the popular combination of penicillin and dihydrostreptomycin produces serious toxicity too often to permit casual administration of it. Where it is pos-

sible to obtain purulent material, titration of the organisms for selective antibiotic sensitivity, although not infallible, is recommended for a more specific selection of a drug. Although systemic administration of antibiotics is invariably most effective, combining them with nasal decongestants used topically in mild nasal infections is useful. The popularity of gamma globulin as prophylaxis against infection is not supported by the facts. Several recent reports indicate that its use is of questionable value.[5] Steroids should rarely, if ever, be used in the presence of infection. When infection develops in a patient receiving a maintenance dose of steroids, the dose should be increased to meet the greater demands for the steroids that the suppressed adrenal cortex cannot meet.

Discussion thus far has been confined to treatment of the acute episode of concomitant infection and allergic disease. It is only natural to expect the allergic symptoms to continue with their characteristic chronicity and for future incidents of infection to arise. This pattern can be anticipated and prevented by management of the allergic factor. A careful and detailed history supplemented by a physical examination must be obtained. Corroboration by skin testing should then follow and a long-range therapeutic regime established. This should include elimination of factors in the environment and in the diet, when warranted, and a course of hyposensitization with a specific antigen administered as indicated by the investigation. In this fashion one can practice truly prophylactic therapy, as proven by a decided reduction or elimination of episodes of infection consequent to improvement of the symptoms of allergic reaction.

From the George Piness, M.D., Allergy Group, 240 South La Cienega Boulevard, Beverly Hills (Bookman).

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